Preparation and Characterization of a Novel Responsive Hydrogel with a β-Cyclodextrin-Based Macromonomer

Yu-Yang Liu, Xiao-Dong Fan

Department of Chemical Engineering, Northwestern Polytechnic University, Xian, People's Republic of China, 710072

Received 14 June 2002; accepted 1 August 2002

ABSTRACT: Based on a combination of poly(*N*-isopropylacrylamide), which could respond to an external temperature, and β-cyclodextrin (β-CD), which could form a molecular inclusion complex, a novel hydrogel, having both thermal and pH sensitivities and containing β-CD and *N*-isopropylacrylamide (NIPA) segments, was synthesized. For the incorporation of β-CD into the polymer network, a macromonomer was prepared first by the reaction of a β-CD-based polymer with maleic anhydride in dimethylformamide and then by copolymerization with NIPA in an aqueous solution. Elemental analysis, IR spectroscopy, differential scanning calorimetry, and swelling measurements were employed for the characterization of the hydrogel chain structure and its physical properties. With methyl orange as a model compound in inclusion tests, it was found that the hydrogel not only possessed a remarkable supramolecular inclusion ability (with respect to that of the small molecule cyclodextrin) but also could sensitively respond to various external stimuli, including the temperature, pH, and ionic strength. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 89: 361–367, 2003

Key words: resins; hydrogels; cyclodextrin; *N*-isopropylacrylamide

INTRODUCTION

Syntheses and characterizations of polymeric controlled-release drug delivery systems have attracted great attention from many polymer scientists in recent years.[1–9] These systems, which are based on biodegradable,[5] pH-sensitive or thermally sensitive polymers,[6–9] are usually first inserted into so-called smart hydrogels and then loaded into therapeutic medicines via polymer chain absorption or a matrix physical trap so that the drug release mechanism can be studied with respect to the functional polymer chain structures and external stimuli.[1–9] Unfortunately, the few polymeric drug delivery systems reported so far not only possess responsiveness to environmental alternations but also can form real molecular inclusion complexes.[10,11] To fill this gap, in a previous publication,[11] we presented a novel thermally sensitive and pH-sensitive hydrogel with a strong supramolecular inclusion capability. The hydrogel was synthesized with *N*-isopropylacrylamide (NIPA), a thermally sensitive component, and β-cyclodextrin (β-CD), a strong molecular inclusion component, and was characterized according to its special macromolecular network structure and responsive properties related to thermal, pH, and ionic strength variations.

To further improve the hydrogel product yield, increase the content of β-CD in the hydrogel, and upgrade its equilibrium swelling ratio (ESR), we present another synthetic strategy for a novel functional hydrogel based on the copolymerization of NIPA and a macromonomer from a maleic anhydride (MAH) modified β-CD resin (MAH/β-CD/EPI, where EPI is epichlorohydrin). This hydrogel, with a higher product yield, shows a molecular inclusion capability, a higher swelling ratio (SR), and excellent mechanical strength during a rapid deswelling process. Moreover, the hydrogel also preserves much better responsive sensitivity when subjected to external stimulus than the previous hydrogel.

EXPERIMENTAL

Materials

NIPA was purchased from Acros (Leicestershire, UK; 99% purity). β-CD was acquired from the Northwestern Geological Institute of China (Xi'an, China) and purified two times by recrystallization from water before use. All other reagents, including ammonium persulfate (APS), sodium bisulfite (SBS), MAH, and EPI, were analytical-grade and were made in China; they were used as received without further purification.

Preparation of the β-CD/EPI resin

The β-CD-based resin was prepared by the condensation reaction of β-CD with EPI in an alkaline solution.

Correspondence to: X.-D. Fan (xfand@yahoo.com).

Contract grant sponsor: Northwestern Polytechnic University Doctorate Foundation.

Contract grant sponsor: Shaanxi Province National Science Foundation.

Journal of Applied Polymer Science, Vol. 89, 361–367 (2003)

TABLE I
Feed and Actual Compositions in Hydrogels

Sample code	Feed composition			Actual composition of NIPA (wt %)[a]
	NIPA/MAH/β-CD/EPI (g/g)	APS (mg)	SBS (mg)	
MN1	0.42/0.18	12.0	5.5	82.3
MN2	0.36/0.24	12.0	5.5	75.6
MN3	0.30/0.30	12.0	5.5	68.4
MN4	0.24/0.36	12.0	5.5	60.8
MN5	0.18/0.42	12.0	5.5	53.0

[a] Calculated from C and N content as measured by element analysis.

Specifically, 21.0 g of β-CD was added to 129.0 g of an aqueous solution containing 11.1 g of NaOH. Then, 17.1 g of EPI was added dropwise at 60°C over 45 min. The reaction was conducted at 60°C for 5 h and at 30°C for 19 h. The final product was precipitated by the addition of a large amount of acetone. The precipitates were repeatedly dissolved in 30 mL of distilled water and poured into 120 mL of acetone several times for the removal of NaCl. The sample obtained was dried at 70°C for 3 days and at 110°C for 6 h in a vacuum oven.

Preparation of the macromonomer

To obtain a macromonomer based on the β-CD/EPI resin that could be copolymerized with NIPA, we designed and synthesized a modified β-CD/EPI resin carrying vinyl carboxylic acid groups. Specifically, 7.5 g of the β-CD/EPI resin was dissolved in 37.5 mL of dimethylformamide, and 3.0 g of MAH was added subsequently. The mixture solution was heated at 80°C for 10 h under vigorous stirring. After the reaction was completed, the mixture was allowed to cool to room temperature, and then 30 mL of acetone was added. A white precipitate was filtered, washed at least three times with a large amount of acetone, and dried at room temperature for 1 day and at 80°C for 3 days in a vacuum oven. From this recipe, 7.30 g of the macromonomer (MAH/β-CD/EPI) was obtained, and its carboxylic group content (2.01 mmol/g) was measured by a titration method.

Synthesis of the hydrogel

The hydrogel was synthesized from NIPA and the macromonomer (MAH/β-CD/EPI) in an aqueous solution at 20°C with an APS and SBS redox system as the initiator. Specifically, 0.6 g of MAH/β-CD/EPI and NIPA were dissolved in 2.4 mL of distilled water, and then 0.5 mL of an SBS solution was added. After nitrogen gas bubbling for 15 min, 0.5 mL of an APS solution was added with an injector. The copolymerization was conducted at 20°C for 24 h. The hydrogel obtained was taken out from the bottle and cut into thin disks 12 mm in diameter. The samples were immersed in distilled water, which was changed every 12 h, for 6 days for the removal of the unreacted monomer. Later, they were dried under ambient conditions for 2 days and at 80°C for 48 h in a vacuum oven. The synthesized hydrogel compositions are listed in Table I.

Instrument analyses

^{13}C-NMR measurements were conducted on a Varian Inova 400 spectrometer (Massachusetts) at room temperature with D_2O as a solvent. IR spectroscopy experiments were preformed on a Specode 75 model (Carl Zeiss, Jena, Germany) with KBr as the sample holder. Elemental analyses were carried out on a Vario EL III instrument (Hanau, Germany). Ultraviolet–visible spectra were recorded on a UV-1200 spectrophotometer (Beijing, China).

Differential scanning calorimetry (DSC; MDSC 2910, TA Instruments, New Castle, DE) measurements were used to determine the hydrogel volume-transition temperature (T_v). The samples were first swollen to an equilibrium state and then heated from 10 to 60°C at a heating rate of 3°C/min. The onset temperature of the thermogram was treated as T_v. All DSC measurements were duplicated for each sample.

Swelling measurements

The hydrogel SR was measured after the samples were swollen to a desired equilibrium state. They were carefully taken out from the solution, wiped with filter paper for the removal of the free water on the surface, and then weighed. SR (g/g) was calculated as follows:

$$SR = (w_1 - w_0)/w_0$$

where w_0 and w_1 are the weights of dry and wet samples, respectively. When a hydrogel reaches its swelling equilibrium state under a fixed condition, its SR is called ESR. All SR measurements were triplicated for each sample.

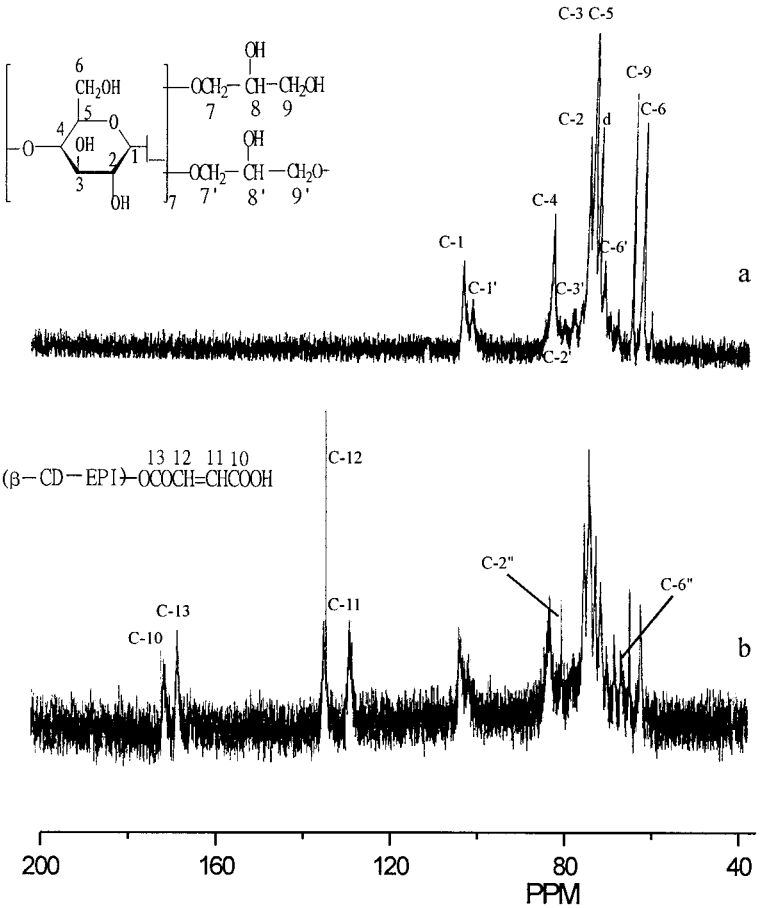

Figure 1 ^{13}C-NMR spectra of (a) β-CD/EPI and (b) MAH/β-CD/EPI macromonomers with D_2O as the solvent (d = C-7, C-8, C-7′, C-8′, or C-9′).

Preparation of the buffer solutions

The buffer solutions used here were prepared according to a previously reported method.[11]

RESULTS AND DISCUSSION

Molecular structure of the macromonomer and hydrogel

A polyfunctional macromonomer was prepared by the reaction of MAH with a β-CD/EPI resin.[11] ^{13}C-NMR spectra of the β-CD/EPI resin and macromonomer are shown in Figure 1(a, b). It can clearly be observed in Figure 1(a) that besides the original chemical shifts of C-2, C-3, and C-6 in β-CD, three new chemical shifts occurred that corresponded to C-2′, C-3′, and C-6′. This indicates that the chemical reactions on the three hydroxyl groups were directly linked to these carbons. The chemical shift of C-1′ was from a substitution on C-2 and C-3 carbons. The chemical shift for C-9 could be assigned as a terminal carbon of 2-hydroxylpropl ether.[12,13] However, there was no evidence for the existence of glycidyl groups in β-CD/EPI. Figure 1(b) presents the ^{13}C-NMR spectrum of the macromonomer, in which chemical shifts of carbonyl carbons (C-10 and C-13) and vinyl carbons (C-11 and C-12) can clearly be observed.[11] The result suggests that vinyl acrylic groups were successfully grafted onto the β-CD resin. Furthermore, because of the formation of ester bonds in β-CD/EPI, the original chemical shifts of C-2 and C-6 were evidently downfield of the C-2″ and C-6″ positions. This further confirms that the reaction was accomplished for this system.

Figure 2 presents ultraviolet spectra from 362.5 to

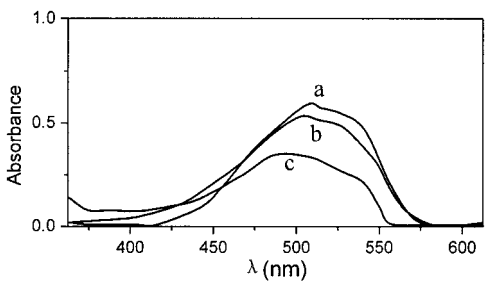

Figure 2 Ultraviolet–visible spectra of MO (2×10^{-5} mol L^{-1}) in the presence of different MAH/β-CD/EPI concentrations: (a) 0, (b) 2, and (c) 8.0 mg/mL.

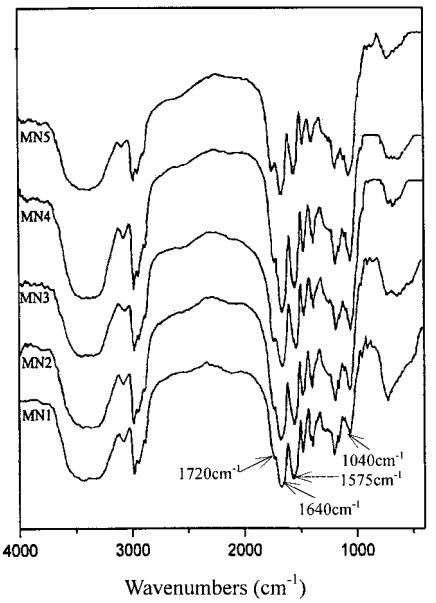

Figure 3 IR spectra of hydrogel samples MN1–MN5.

612.5 nm for methyl orange (MO) with different contents of the macromonomer in a pH 2.0 buffer solution. The absorbance band for pure MO appeared at 507 nm; however, with the addition of the macromonomer, its peak intensity not only decreased but also shifted to a lower wave-number region. The results indicated that the macromonomers still possessed the capability of forming molecular inclusion complexes because similar results could be observed for a pure β-CD/MO system.[14,15]

IR spectra of the hydrogels (Fig. 3) show a strong C—OH stretching vibration around 1040 cm^{-1} and a C═O stretching vibration around 1720 cm^{-1} from the MAH/β-CD/EPI segment. A C═O stretching vibration around 1640 cm^{-1} and an N—H deformation vibration around 1575 cm^{-1} from the poly(*N*-isopropylacrylamide) (PNIPA) component can also be seen. A strong and wide band at 3250–3600 cm^{-1} represents a combination of the absorptions of amide and hydroxyl groups from both MAH/β-CD/EPI and NIPA, respectively.

Influence of pH on the hydrogel ESR

Figure 4 presents the influence of pH on the hydrogel ESR. Clearly, ESRs for samples MN1–MN5 exhibited a marked transition region around pH 4.0, and the values also increased with an increase in pH. This result may be attributed to the character of —COOH groups in the hydrogels. At low pHs, the unionized —COOH groups could form hydrogen bonding via intramolecular and intermolecular interactions[1,8,9,11,16] and, as a result, could lead to lower ESR values for the hydrogels. However, with increasing pH, the —COOH groups began to ionize; the ionized carboxylic groups not only could maintain a good hydrophilic character for the hydrogels but also could produce electrostatic repulsive forces inside the samples. This action could effectively produce hydrogel expansion and cause the ESRs to reach relatively larger values.[1,8,9,11,16] Moreover, as shown in Figure 4, the effect of pH on ESR also depended on the concentration of —COO^- groups; the higher the content was of —COOH, the more sensitive the hydrogel response was to pH. The sequence of pH sensitivity for the samples followed this order: MN1 < MN2 < MN3 < MN4 < MN5.

Influence of temperature on the hydrogel ESR

Usually, for an NIPA-based copolymer carrying —COOH groups, the thermosensitivity strongly depends on its medium pH and —COOH groups in the polymer network.[1,8,9,11,16] This can also be demonstrated in Figure 5(a–c), which shows the effect of temperature on the hydrogel ESR at different pH values. Moreover, to exactly detect T_v for the samples, we conducted swelling DSC measurements,[8,17] and their DSC thermograms and individual T_v values are shown in Figure 6. Evidently, according to both DSC and ESR experimental methods, all the samples exhibited a distinct volume phase transition in agreement with T_v. The transition also tended to become sharper with an increase in the NIPA content at the same pH value. Similar results were observed at other pH values. Interestingly, T_v at pH 5 shifted to a higher temperature region than T_v at pH 3.0 and was slightly different than T_v at pH 7.4. The results suggest that, at higher pH values, electrostatic repulsive forces between ionized —COOH groups, which could be affected greatly by the medium pH, could have effectively offset the chain aggregation caused by the temperature-sensitive component. As a result, the T_v values of the hydrogels shifted to a higher temperature region.[1,9,11,16] The larger the content was of —COOH groups, the higher T_v could be. In addition, a hydrophobic interaction between isopropyl groups

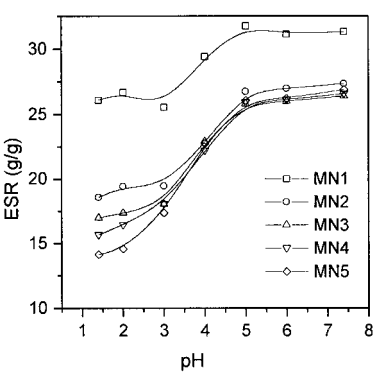

Figure 4 Influence of the pH value on ESRs of hydrogel samples MN1–MN5 synthesized at 24.5°C.

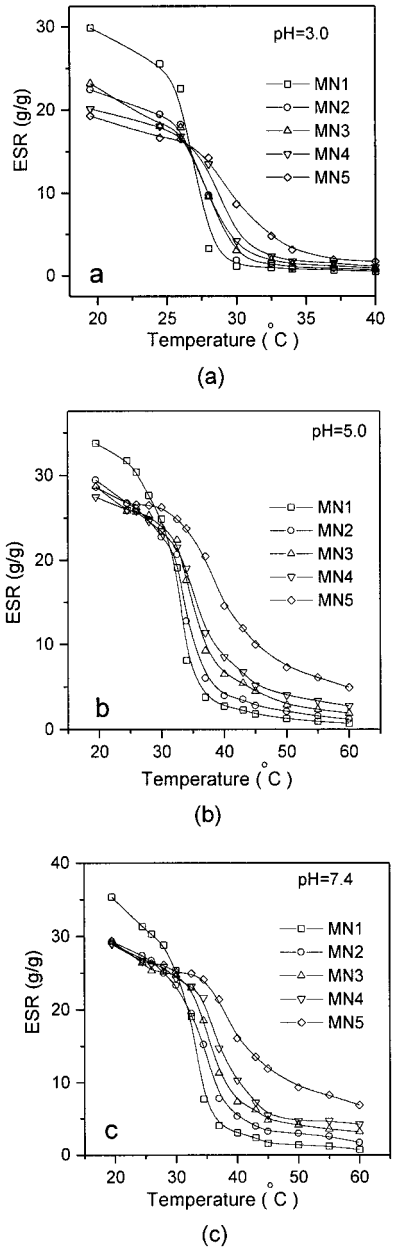

Figure 5 ESR as a function of temperature at (a) pH 3.0, (b) pH 5.0, and (c) pH 7.4 for samples MN1–MN5.

in NIPA and cavities in β-CD could also occur when the hydrogels shrank after an increase in the surrounding temperature. However, this interaction might not have greatly affected the temperature sensitivity of the PNIPA component; as shown in Figures 5 and 6, NIPA units in the hydrogels still exhibited clear T_v values related to the lower critical solution temperature (LCST) and presented distinct thermosensitivity.

Influence of the ionic strength on the hydrogel ESR

Figure 7 shows ESR values of the hydrogels as a function of the NaCl concentration at 24.5°C. Two ESR transitions can be observed, with NaCl concentrations changing from 10^{-5} to 2.0*M*. The first transition took place in dilute NaCl solutions. Under this condition, the hydrogel shrinkage was a continuous process, and ESR decreased quickly with the change in the NaCl concentration. The results could possibly be inter-

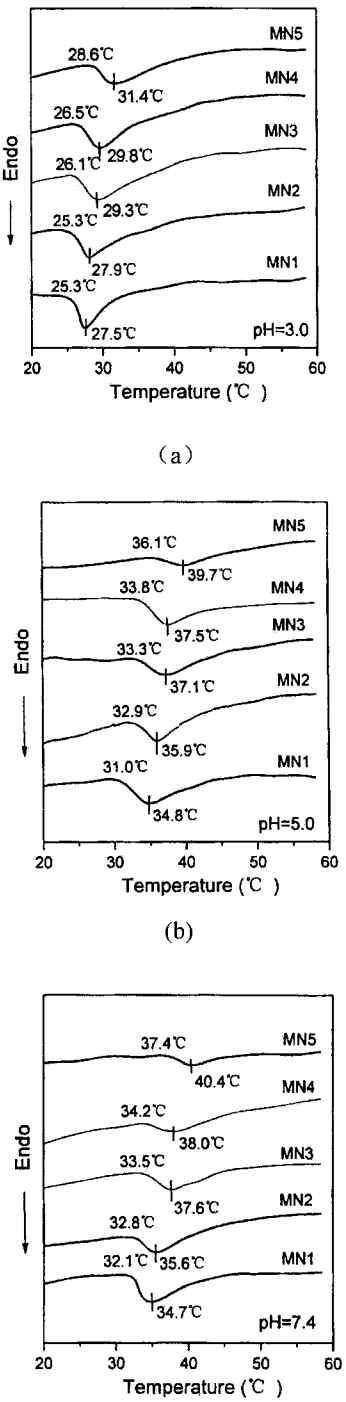

Figure 6 DSC thermograms of MAH/poly(β-CD/EPI)/NIPA with variations of the NIPA content in the polymer at (a) pH 3.0, (b) pH 5.0, and (c) pH 7.4 (ionic strength = 0.1).

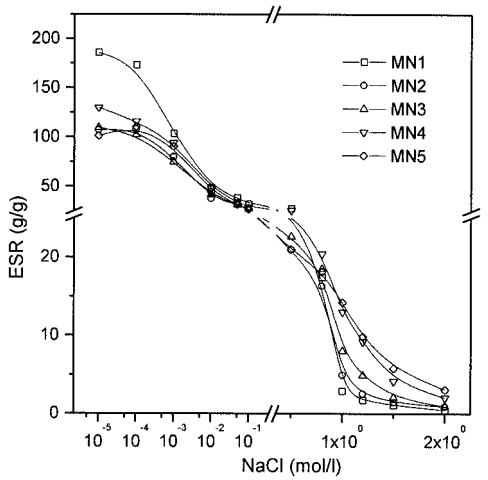

Figure 7 ESR as a function of the ionic strength in distilled water at 24.5°C for samples MN1–MN5.

preted as an osmotic deswelling process inside the hydrogel, which might have been caused by some counterions and Donnan equilibrium effects.[11,18,19] The second transition occurred in concentrated NaCl solutions. Under these conditions, the hydrogel ESR decreased relatively slowly with respect to that for the dilute NaCl solution. The results could be attributed mainly to the higher ionic strength, which could markedly lower LCST of the PNIPA component;[19,20] consequently, it could trigger the hydrogels to shrink at a temperature that could still be under the original LCST. This analysis is further confirmed by Figure 7, which shows the hydrogel transition region increasing to a higher NaCl concentration after a decrease in the NIPA content.

Hydrogel dynamic swelling behavior under different pHs and temperatures

To investigate if the synthesized hydrogel could reversibly respond to changes in pH and temperature

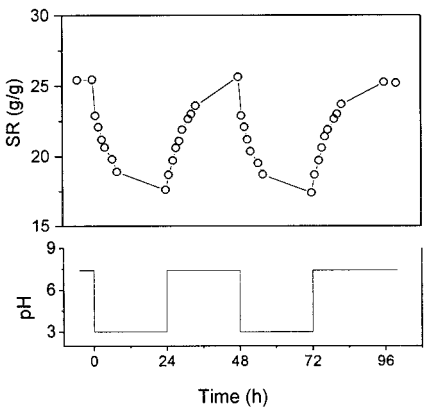

Figure 8 Oscillatory swelling behavior as a function of time and pH at 24.5°C for sample MN3.

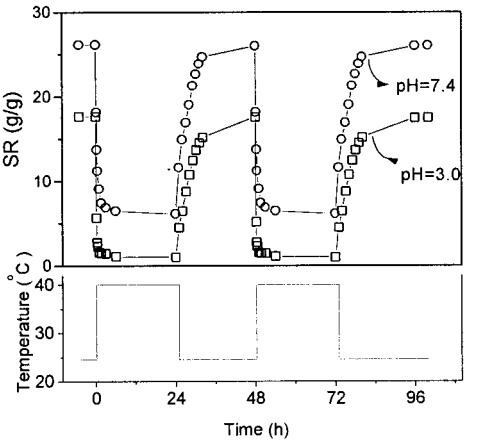

Figure 9 Oscillatory swelling behavior as a function of time and temperature at pH 7.4 and pH 3.0 for sample MN3.

and to determine how fast its responsive rate was,[8] we conducted the oscillatory swelling experiments shown in Figures 8 and 9. Figure 8 clearly shows that sample MN3 reversibly responded to the alternation of pH between 7.4 and 3.0. Figure 9 shows that sample MN3 responded well to alternations of temperature between 24.5 and 40.0°C at pH 3.0 and pH 7.4, respectively. As can be seen in Figure 9, under weak acid (pH 3.0) and weak base (pH 7.4) conditions, the sample presented a fast shrinking rate at 40°C. For a reversal process, the swelling rate of the sample was relatively slower. This may suggest that the swelling process of hydrogels is a rate-related diffusion process.[21]

CONCLUSIONS

A novel macromonomer was prepared from an MAH-modified β-CD resin synthesized by the condensation polymerization of β-CD and EPI in an alkaline solution. The macromonomer possessed the capability of forming molecular inclusion complexes.

By the copolymerization of the macromonomer with NIPA, novel hydrogels [poly(MAH/β-CD/EPI-*co*-NIPA)] were synthesized with free-radical polymerization with a redox system as the initiator. The hydrogels, containing different NIPA and β-CD components, showed clear values of T_v with pH and ionic strength sensitivities.

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